Reprinted from "Clinical Proceedings," Vol. 5 No. 5, 1946

EXPERIMENTAL DIABETES

B. A. Houssay, M.D.

Institute of Physiology, Faculty of Medicine, Buenos Aires.

Advancement in the knowledge of pancreatic function, the discovery of insulin and the modern treatment of diabetes are the result of experimental studies of this disease. Further and no less important benefits can be expected from the continuance of these studies. In this paper problems now occupying experimental scientists will be presented to the general practitioner, specially emphasizing the practical results so far obtained. Only an outline of the work being done can be given. Metabolic disturbances producing a simple transitory hyperglycaemia, such as those due to injection or secretion of adrenaline or other hormones and drugs, or stimulating of nerve centres, as occurs after puncturing the medulla, will not be considered. It will be understood there is a true diabetic condition only when there is permanent hyperglycemia together with severe metabolic changes: fasting hyperglycaemia and glycosuria, a typical prolonged sugar tolerance curve, changes in the R.Q. hyperketonaemia and ketonuria, loss of weight, cachexia, etc.

PANCREATIC DIABETES AND INSULIN

Diabetes was produced experimentally for the first time by von Mering and Minkowski in 1889, by total extirpation of the pancreas in the dog. This experiment proved that diabetes is due to pancreatic insufficiency. Diabetes is caused by the suppression of the internal secretion of the pancreas, as the following experiments have shown:

(a) Pancreatic grafts prevent the onset of diabetes if performed at the same time as the removal of the organ; and correct the diabetic alterations, if the graft is made when diabetes has already developed.

(b) Venous blood coming from the pancreas, produces hypoglycaemia.

(c) Insulin, the hormone obtained from the pancreas, prevents the appearance of, or corrects, diabetes and permits pancreatectomized dogs to survive many years if they are adequately fed (Hedon, Chaikoff and Kaplan, 1927).

Banting and Best's 1922 experimental studies led to the discovery of insulin; increased knowledge of carbohydrate metabolism and diabetes, and gave the foundation for dietetic and insulin treatment of the disease.

Insulin is secreted by the Langerhans islets of the pancreas. This is proved by 2 principal facts:

1. Atrophy of the glandular acini, induced by ligature of the pancreatic

duct, does not produce diabetes as long as the islets remain in good condition (Szobolew).

2. Severe lesions producing atrophy of the islets provoke a complete diabetic state, even when the acini are in good condition ; this selective suppression of β cells of the islets can be obtained by means of anterior hypophyseal extract and alloxan ; also in certain conditions by thyroid feeding.

Benign and malignant hyperplasia of the Langerhans islets, giving an excessive secretion of insulin, produce symptoms of hyperinsulinism. Hypoglycaemic crises, typical of this condition, can be suppressed by removal of the islet tumours or ample resection of the pancreas. Liver metastases of these tumours contain insulin.

The liver is indispensable for the establishment of diabetes, whatever the diabetogenic factor, even after pancreatectomy. It is also necessary for the continuance of the diabetic condition, since hepatectomy is followed by a fall in the blood sugar from the high diabetic level to a fatal hypoglycaemia (Mann *et al.*).

Between 1922 and 1930 it was commonly accepted that the pancreas was the only important factor in the pathogenesis of diabetes. The part played by the liver in the production of sugar and the regulation of the blood sugar level was demonstrated later, as also the importance of other endocrine glands.

HYPOPHYSEAL AND METAHYPOPHYSEAL DIABETES

The frequent existence of diabetes in acromegaly has been known for a long time. Atkinson states that 32.8% of cases of acromegaly reported in the literature up to 1938 had glycosuria or diabetes. The diabetogenic role of the anterior lobe of the hypophysis was first demonstrated in 1930 in my Institute. Hypophysectomy increases sensitiveness to insulin (Houssay and Magenta, 1924 and 1929), due to removal of the *pars distalis*, commonly called the anterior lobe in mammals. This hyper sensitiveness can be corrected by injection of the anterior lobe extract (Houssay and Potick, 1929).

Later, in 1930, Houssay and Biasotti showed that removal of the hypophysis or the *pars distalis* alone improves pancreatic diabetes in the dog and toad and phloridzin diabetes in the dog. In the toad, implantation of the *pars distalis* is followed by an increase in the severity of the diabetic symptoms to the level existing before hypophysectomy or even more. The diabetogenic activity of the hypophysis has thus been completely demonstrated.

The diabetogenic activity of the anterior lobe (*pars distalis*) of the hypophysis of mammals was demonstrated in 1932 in 3 laboratories*.

*By Evans, Meyer, Simpson and Reichert in California ; by Bauman and Marine in New York and by Houssay, Biasotti, Di Benedetto and Rietti in Buenos Aires.

Since then it has been a major subject of study in the Institute of Physiology of the Buenos Aires Faculty of Medicine.

Hypophyseal diabetes must be distinguished from metahypophyseal diabetes. Hypophyseal diabetes is produced by the injection of anterior lobe extract and rapidly disappears on discontinuing the treatment for 1 or 2 days. Though there is hyperglycaemia, the islets are not yet severely damaged and the pancreas secretes insulin (Houssay, Foglia, Smyth, Riett, Houssay, 1944). Later the damage is more severe and insulin secretion is considerably reduced or even suppressed. The lesions observed consist in reduction of the granules, hydropic degeneration and pyknosis of the β-cells. These alterations are reversible and they disappear when the treatment is discontinued. Insulin secretion is also re-established.

When the treatment with anterohypophyseal extract is more prolonged, the lesions are even more severe and become irreversible. The β-cells disintegrate and disappear and the islets atrophy. When the injections are discontinued the animals do not recover, remaining with a permanent diabetes. I have called this condition a metahypophyseal diabetes. It is a pancreatic diabetes due to insufficiency of the Langerhans islets, provoked by the anterohypophyseal extract, but not maintained by this extract. This permanent metahypophyseal diabetes was first demonstrated in dogs with a subtotal pancreatectomy (Houssay, Biasotti and Rietti, 1932) and later in dogs with a whole pancreas (Young, 1937). Young's work on this form of diabetes is particularly important. Table I gives a summary of the principal differences between hypophyseal and metahypophyseal diabetes.

TABLE I

	Hypophyseal Diabetes	*Metahypophyseal Diabetes*
Anterior lobe extract injections	Necessary to maintain the condition, which disappears on discontinuing treatment.	Unnecessary to maintain the condition, which persists after discontinuing treatment.
Damage to β-cells	Reversible	Irreversible
Resistance to insulin	Greatly increased	Not increased, as in pancreatic diabetes.
Liver glycogen	High or normal*	Low
Course	Cure or onset of metahypophyseal diabetes	Permanent and progressive

*It decreases only when there is considerable hyperglycaemia (250 to 300 mg. per 100 cc.

The diabetogenic effect can be obtained with smaller doses of antero, hypophyseal extract when the pancreas is partially removed (Houssay-Biasotti and Rietti, 1932-34). It is also more easily provoked by a second or third series of injections of anterohypophyseal extract that follows the previous one after a few days interval. Pancreatic resistance is diminished when the number of islets is reduced or the β-cells are damaged. Two factors are responsible for the production of this diabetes : hyperglycaemia and damage to the islets.

The role of hyperglycaemia can be demonstrated in several ways. Diabetes is not produced if the animals are kept fasting ; on the contrary, it is easily provoked when a diet rich in saccharose is given (Houssay and Biasotti). The diabetic state is preceded by an initial hyperglycaemia, extrapancreatic in origin, since it can be seen very plainly in the hypophysectomized pancreatectomized animal. This form of diabetes can be prevented or cured during the first stages by means of hypoglycaemic agents such as insulin or phloridzin (Lukens and Dohan, 1942).

The damaging effect of the anterohypophyseal extract has also been demonstrated. Hyperglycaemia maintained during 4 days by intravenous injection of glucose does not alter the islet cells nor does it diminish insulin secretion in dogs. On the other hand severe lesions of the β-cells together with complete or almost complete suppression of insulin secretion are observed when hyperglycaemia of a similar degree is produced by injection of anterohypophyseal extract (Houssay, Foglia, Smyth, Rietti and Houssay, 1941). This extract also produces fatty degeneration of the liver, and the acini and fine ducts of the pancreas, and other alterations.

Hypophyseal diabetes, the condition existing while the anterohypophyseal treatment is maintained, commences by an extrapancreatic phase to which a progressive insufficiency of the islets is added, due apparently to the exhaustion of the cells in the effort to cope with the hyperglycaemia. Initial hyperglycaemia is due to the excess production of sugar by the liver and the diminished consumption of glucose brought about by the hypophyseal factor. The result is a hyperglycaemia with a low R.Q., excess fat catabolism and increased ketogenesis. A notable characteristic of hypophyseal diabetes is a marked increase in resistance to insulin.

Metahypophyseal diabetes is a simple pancreatic diabetes due to progressive destruction of the Langerhans islets. Its course is similar to Sandmeyer's diabetes produced by subtotal pancreatectomy, but usually its severity increases more rapidly.

ADRENAL DIABETOGENIC ACTIVITY

The following are the more important facts in favour of the adrenals having a diabetogenic effect.

(a) Adrenalectomy diminishes the severity of symptoms in pancreatic diabetes in cats, rats and toads (Long and Lukens, Houssay and Biasotti, Foglia and Rietti).

(b) Diabetes is seen in certain cases of hyperinterrenalism, of Cushing's disease and the Achard-Thiers syndrome (diabetes in bearded women).

Adrenal cortical extracts and hormones increase the severity of symptoms in animals with a pancreatic diabetes which has been attenuated by adrenalectomy or hypophysectomy (Long *et al.*, Gaunt *et al.*). These substances also increase glycosuria in fasting phloridzinized rats (Kendall *et al.*).

Ingle (1941) observed marked hyperglycaemia and glycosuria in normal rats fed with a diet rich in carbohydrate, when they were injected with large doses of 11-dehydro-17-hydroxycorticosterone during several days. Up to now permanent diabetes has not been obtained by this method, perhaps because the treatment has not been sufficiently prolonged or the rat is not suitable for this demonstration. Repeated injections of diethylstilbestrol also produce glycosuria even after removal of the hypophysis and adrenals (Ingle, 1944). Recent studies on this subject have been reviewed by Long (1942) and Houssay and Deulofeu (1943).

THYROID AND METATHYROID DIABETES

Thyroid administration does not produce diabetes in animals with an intact pancreas and in good general condition (Houssay and Brignone). Sometimes a transitory hyperglycaemia of not more than 149 mg. per 100 cc. has been observed in the dog. The Langerhans islets become hypertrophied in many species.

Reduction of the pancreatic tissue, by surgical removal of 6-7 or 7-8 of its mass, sensitizes the animal to thyroid treatment and a permanent diabetic condition is produced after a few weeks of thyroid treatment and a permanent diabetic condition is produced after a few weeks of thyroid feeding (De Finis and Houssay, 1944). The blood sugar rises, glycosuria, ketonuria and other diabetic symptoms appear. The β-cells of the islets show progressive alterations, the granules diminish, hydropic degeneration, pyknosis and cytolysis follow each other bringing about complete disappearance of the cells and atrophy of the islets.

Discontinuance of the thyroid treatment during the first stages is followed by a rapid return to a normal blood sugar, disappearance of all diabetic symptoms and recovery of the β-cells not already completely destroyed. A more prolonged thyroid treatment produces a severer destruction of the cells, in which case the damage to the islets is irreversible and on discontinuance of the treatment the animal does not recover, but remains permanently diabetic. This diabetes appears during the thyroid treatment and because it disappears on discontinuance of the treatment, it is called by us *thyroid diabetes*. Among its symptoms are

noticeable polyuria, frequently marked ketonuria and a moderate increase in insulin resistance. The mechanism of its production is not yet sufficiently well known. Probably 2 factors concur to alter the islets :

(a) Hyperglycaemia.

(b) The toxic action of the thyroid.

Hyperglycaemia is probably of extrapancreatic origin and gradually exhausts the islets, so that a pancreatic insufficiency is added. One of the first alterations to occur is a disturbance in the formation of liver glycogen from sugar, which brings about a decrease in the store of hepatic glycogen. A toxic action of the thyroid is probably added to the damaging effect of hyperglycaemia, since it is well known that in hyperthyroidism progressive lesions are observed in several organs, notably in the liver and in the heart.

The diabetes persisting after discontinuance of the thyroid treatment is called by us, metathyroid diabetes. It is a diabetic condition due to insufficiency of the Langerhans islets provoked, but not maintained, by thyroid treatment. We have obtained it in 19 dogs with a subtotal pancreatectomy ; it did not occur in controls which had undergone a similar operation, but were not treated with thyroid. Other controls were fed for 1 month powdered liver, kidney or muscle instead of thyroid, and did not develop diabetes. This diabetogenic effect of the thyroid was observed after removal of the sexual glands, the thyroid and the adrenal medulla

The diabetogenic effects of the anterohypophysis and the thyroid usually reinforce each other, but the association has a severe toxic action. This compound treatment produced a permanent diabetes in 3 dogs each with an intact pancreas. By grafting the pancreatic glands of these animals into the circulation of a diabetic dog it was possible to demonstrate that they did not secrete insulin.

The diabetogenic action of the thyroid is thus completely demonstrated but it is not as intense as that of alloxan or anterohypophyseal extract. Thyroid treatment can only produce diabetes in animals with a pancreas reduced by surgical removal of a great part of its mass, or already damaged by a previous treatment with anterohypophyseal extract or thyroid. It cannot do so in animals with an intact and healthy pancreas.

In man, hyperthyroidism increases the severity of diabetes and the same occurs, nearly always, when a diabetic patient is given thyroid treatment. Therefore in man similar effects to those observed in other species can be seen : an excess of thyroid produces an extrapancreatic metabolic effect, which increases the severity of diabetes and diminishes the effect of insulin ; also it can further damage a pancreas with a previously reduced resistance.

Hyperthyroidism is not more frequent in diabetics than in the general population. On the other hand diabetes is twice as frequent in hyperthyroids as in the general population (John, 1942). This also is in agree-

ment with experimental results showing the thyroid has a definite though weak diabetogenic activity.

Thyroid insufficiency does not improve experimental diabetes in the dog. In human diabetes sugar tolerance is somewhat improved, glycosuria diminishes and the dose of insulin necessary to control the condition is decreased. The improvement is not greater than that which can be obtained by diet and insulin treatment and certainly does not justify a thyroidectomy. This operation produces myxoedema, a condition far more troublesome than diabetes, and it is not a good therapeutic result to leave a patient with 2 diseases instead of 1.

Hyperthyroidism in diabetics should be actively treated by iodine, thiouracil or subtotal thyroidectomy. The majority of the cases are considerably improved.

ALLOXAN DIABETES

Shaw Dunn and his collaborators showed that alloxan injections produce necrosis of the Langerhans islets, with pyknosis and lysis of the β-cells and subsequent atrophy of the islets, with conservation of the β-cells. This has been demonstrated in rabbits (Shaw Dunn, 1943 ; Bailley and Bailey, 1943 ; Hughes, Ware and Young, 1943 ; Kennedy and Young, 1944 ; Goldner and Gomori, 1944), rats (Gomori and Goldner, 1943 ; Thorogood, 1944), dogs (Carrasco-Formiguera, 1943 ; Goldner and Gomori, 1944), monkeys, etc. In man it has not been observed in cases injected with alloxan (Brunschwig *et al.*, 1944 ; Joslin, 1944) probably because the dose given was too small, or because there was habituation. In my laboratory the action of alloxan has been studied by Orias, Brignone, Martinez, Sara and Di Pietro in rats, cats, dogs, rabbits, guinea pigs and toads.

The effects of this drug are not limited to the islets. There is a triphasic effect on the blood sugar. After an initial hyperglycaemia of short duration, there is hypoglycaemia during several hours ; it can be sufficiently marked to be fatal. Later alloxan diabetes appears. Glucose administration prevents death from hypoglycaemia and facilitates the appearance of a permanent diabetes. Mortality is very high during the first days, and there are necrotic lesions in the kidneys, liver, etc. Larger doses produce nervous symptoms. Renal and hepatic lesions rapidly disappear if the animal survives, but atrophy of the Langerhans islets is usually marked and irreversible, so the animals frequently remain with a permanent diabetes. According to the terminology so far employed, this condition should be called meta-alloxan diabetes, since it is a diabetes due to islet insufficiency provoked, but not maintained, by alloxan.

Hypophyseal and thyroid diabetes are due to islet lesions produced by the conjoint effect of hyperglycaemia and the toxic action of the drug on the β-cells. Alloxan diabetes is due solely to a toxic action which is

intense and immediate ; the alloxan injected disappears from the circulation in 5 minutes. For this reason treatment of the initial hyperglycaemia with insulin, phloridzin or fasting, does not prevent the appearance of alloxan diabetes (Goldner and Gomori, 1944). A single dose of alloxan is sufficient to produce degeneration of the islets. This contrasts with the need for repeated doses of anterohypophyseal extract or thyroid to obtain the same effect. There is also an "all or none" phenomenon ; a given dose either produces diabetes or has no apparent effect.

This type of alloxan or meta-alloxan diabetes has been obtained so far in rabbits, dogs and rats.

DIABETES DUE TO SUBTOTAL PANCREATECTOMY

Subtotal pancreatectomy does not produce diabetes in the dog if 1-7 to 1-8 of the pancreas is left, provided that insulin treatment is given during the first week following operation and aseptic precautions are rigorously observed. When the amount of gland left is smaller, frequently a mild diabetes occurs. In some cases the blood sugar returns to normal and glycosuria ceases. The islets are in good condition or may show signs of hyperplasia. In other cases the initially mild diabetic condition (Sandmeyer's diabetes) gradually increases in severity until the animal dies with all the symptoms of a diabetes due to total pancreatectomy. A mild diabetes is never stabilized ; either it regresses and disappears or progresses and becomes increasingly severe.

Metahypophyseal and metathyroid diabetes are similar to Sandmeyer's diabetes, since they follow a progressive course, with increasing severity, though usually they are more marked in the initial phases. In these cases the damage to the β-cells is not complete at the beginning, but increases with time. The cells become gradually altered and disappear one after the other.

All forms of mild diabetes become worse with diets rich in carbohydrates. A normal dog can be fed any amount of sugar without becoming diabetic ; but a dog with a subtotal pancreatectomy, having a normal blood sugar and no glycosuria, can be made diabetic by feeding it with sugar, as was shown by Allen (1913), a fact we have repeatedly confirmed.

After removing 95% of the pancreas from a rat, the blood sugar remains normal for 2 or 3 months. After this lapse a diabetic condition appears which increases gradually in a way similar to Sandmeyer's diabetes in the dog, but less rapidly in spite of the marked hyperglycaemia and glycosuria. The prolonged prediabetic stage, with no glycosuria is very remarkable in this species. Foglia (1944) has made a systematic study of this type of diabetes.

PHLORIDZIN DIABETES

Phloridzin is a glucoside which, injected into animals, produces intense

glycosuria. The condition, called phloridzin diabetes, is complex and has to be examined in detail. There is never hyperglycaemia, and frequently the blood sugar is below normal Glycosuria is due to incapacity of the kidney tubules to reabsorb the sugar filtered through the glomerulus. When the injections are repeated the continuous loss of sugar produces metabolic disturbances similar to those seen in pancreatic diabetes. In phloridzin diabetes there is an excess production of sugar, which is not used by the organism but is lost. In chronic intoxications by phloridzin, ketogenesis increases, the R.Q. is low and there are many other symptoms of a severe metabolic disturbance similar to diabetes. Glucose injection is followed by a more prolonged hyperglycaemia than in normal animals and less glycogen is formed in the muscles.

This diabetic condition produces lesions in several organs, amongst others, in the pancreas. On the fifth day of phloridzin treatment the pancreas was found to secrete insulin normally in 2 dogs ; less than normally in 5 animals ; in 1 case there was no insulin secretion, as demonstrated by the method of grafting the gland into the circulation of a diabetic dog. Administration of glucose to phloridzinised animals is followed by an increase in the R.Q. and formation of muscle glycogen in greater amounts than in pancreatectomized dogs. These observations show that phloridzinised animals probably secrete a certain amount of insulin.

GENERAL DISCUSSION

Metahypophyseal, metathyroid and meta-alloxan diabetes show that the endocrine function of the pancreas is performed by the Langerhans islets, since the destruction of the islets produces diabetes just as when the whole pancreas is removed. In all these cases the pancreatic acini are microscopically normal, but there are severe lesions in the β-cells of the islets, which at first lose their granules, then undergo hydropic degeneration and finally disintegrate, with subsequent atrophy of the islets. In all cases of diabetes there is insufficiency of the endocrine part of the pancreas, which is incapable of secreting the amount of insulin required by the organism. Even when the condition is initiated by extrapancreatic factors, as occurs in hypophyseal diabetes, a few days later hyperglycaemia has begun and the internal secretion of the pancreas diminishes.

The surgical reduction of the pancreatic mass (therefore of the number of islets) diminishes the latter's resistance to the diabetogenic action of sugar and of agents that conjointly with hyperglycaemia damage the pancreas (anterohypophysis, thyroid). The decrease in insular reserve facilitates the action of those substances which must be given repeatedly to be effective. Alloxan, on the other hand, has the same activity in the subtotally pancreatectomized dog as in the normal animal, and less in the subtotally pancreatectomized rat, than in normal ones ; it acts directly

when it reaches a sufficient concentration in the blood.

Repeated or persistent hyperglycaemia is an important cause of damage to the islets, as is seen when sugar, anterohypophysis or thyroid are repeatedly given. In these cases hyperglycaemia is initially due to extra-pancreatic factors but later the hyperglycaemia itself damages the islets. As an increase in blood sugar stimulates the β-cells it is supposed that at first there is hypersecretion, then functional exhaustion followed by damage and final destruction.

In hypophyseal diabetes 2 factors occur to damage the islets, hyperglycaemia and the toxic action of the anterohypophyseal extract. Hyperglycaemia is a necessary condition since there is no diabetes or damage to the islets if hyperglycaemia is prevented by keeping the animal without food or by injecting insulin and, on the contrary a diet rich in carbohydrate favours the appearance of diabetes (Houssay and Biasotti). Metahypophyseal diabetes can be cured during the first weeks and up to 3 months after onset, in the cat, as long as the β-cells are only damaged and not totally destroyed (Lukens and Dohan). This result can be obtained by a treatment preventing hyperglycaemia (insulin or phloridzin) or by adrenalectomy (Lukens and Dohan). These treatments are no longer efficacious once the majority of the β-cells have been destroyed and irreversible atrophy of the islets has occurred.

The direct toxic action of the anterohypophyseal extract is added to the effect of the hyperglycaemia*. This extract provokes fatty degeneration of the liver, of the small ducts and acini of the pancreas, etc., and death if given in sufficient doses. After treatment for 4 days with doses sufficient to produce diabetes there are marked lesions in the β-cells and a considerable decrease of insulin secretion. On the other hand a similar hyperglycaemia maintained for 4 days by continuous intravenous injection of glucose does not damage these cells nor does it diminish insulin secretion in the dog (Houssay, Foglia, Smyth, Rietti and Houssay). The factors are therefore equally necessary to damage the islets : hyperglycaemia and the direct toxic action of the extract.

Alloxan diabetes is the prototype of a condition produced by toxic destruction of the islet cells. This drug, as soon as it reaches a sufficient concentration in the blood, almost immediately destroys the β-cells. If this destruction is sufficiently widespread, permanent diabetes is the consequence ; if a sufficient number of cells resist and recover, diabetes disappears in a few days.

The islet lesions in pancreatic diabetes can be primary or secondary. Alloxan has a primary effect. It acts directly on the islets, as is shown by the rapidity and selectiveness with which it damages the β-cells. On the other hand, the effects of the anterohypophysis and the thyroids are

*In the case of thyroid diabetes this same effect is produced by the thyroid treatment.

indirect ; first extrapancreatic disturbances occur and later the pancreas is affected. Alloxan diabetes is a pancreatic diabetes from the beginning, while hypophyseal and thyroid diabetes begin by an extrapancreatic phase and only later produce pancreatic diabetes.

An existing insular lesion can be primary or secondary. In the first case the damaging agent acts directly on the β-cells ; in the second a hormonal agent (hyperpituitarism, hyperthyroidism) produces hyperglycaemia and lesions in the islets. In time both these types of diabetes become identical, both are due to pancreatic insufficiency and only by knowledge of the animal's history can the origin be established.

An interesting feature in subtotal pancreatectomy in the rat is the fact that it does not produce diabetes immediately but only after 2 or 3 months, during which the animal has a normal blood sugar. This lapse in the life span of a rat is equivalent to several years in human life. Later a progressive and severe diabetes will inevitably follow. It is possible, therefore, that in man manifest diabetes is also preceded by a prediabetic period without symptoms. If this does occur there would be great advantages in being able to diagnose the condition, and so prevent its progress by maintaining or increasing the functional capacity of the degenerating pancreas. Studies in this direction might be of extraordinary importance for the prevention of diabetes.

Up to now it has not been possible to provoke an experimental diabetes which remains stable at a certain degree of insufficiency. Experimental diabetes either progresses towards a cure or, more frequently, gradually increases in severity, though sometimes the animals survive for a long time. One same agent (anterohypophysis or thyroid) can produce either hyperplasia or degenerative lesions of the islet cells, according to which animal species is used, the dose given, the amount of pancreas present or its anatomical and functional condition.

In some animals the pancreas is remarkably resistant to damaging agents. By repeated injections of small doses of alloxan it is possible to increase the resistance to its toxic effects (Orias).

REFERENCES

Allen, F. M. (1922) : J. Metab. Res. **1.** 5, 53, 57, 89.

Atkinson, F. R. B. (1938) : Endokrinologie. **20.** 245.

Banting, F. G., and Best, C. H. (1922) : J. Lab. Clin. Med. **7.** 464.

Brignone, R. (1944) : Thesis Fac. Med. Bs. Aires.

De Finis, M. L., and Houssay, B. A. (1943) : Rev. Soc. Argent. Biol. **19.** 94.

Foglia, V. G. (1944) : Rev. Soc. Argent. Biol. **20.** 21.

Foglia, V. G., and Souto Maior, M. C. (1941) : Rev. Soc. Argent. Biol. **20.** 55, 79, 163.

Goldner, M. G., and Gomori, G. (1944) : Proc. Soc. Exper. Biol. Med. **55.** 73.

Hedon, E. (1927) : J. Physiol. Path. Gen. **25.** 1.

Hedon, E. (1929) : C. R. Soc. Biol. **100.** 698.

Houssay, B. A., and Deulofeu, V. (1943): Ann. Rev. Physiol. **5.** 373.
Houssay and collaborators. *See* Rev. Soc. Argent. Biol. of the years quoted in the text.
Ingle, D. J. (1944): Endocrinol. **29.** 649, 838.
Ingle, D. J. (1944): Endocrinol. **34.** 361.
John, H. J. (1942): J. Clin. Endocrinol. **2.** 264.
Long, C. N. H. (1942): Ann. Rev. Physiol. **4.** 465.
Lukens, F. D. W., and Dohan, F. C. (1941): J. Clin. Invest. **20.** 444.
Lukens, F. D. W., and Dohan, F. C (1942): Endocrinol. **30.** 175.
Lukens, F. D. W., and Dohan, F. C (1943): Endocrinol. **32.** 475.
Von Mering, J., and Minkowski, O (1889): Arch. Exper. Path. **26.** 371
Orias, O. (1944): Rev. Soc. Argent Biol. **20.** 199.
Shaw Dunn, J. S., and colleagues (1943) Lancet. 1484.
Shaw Dunn, J. S., and colleagues (1943) J. Path. Bact. **55.** 245.
Young, F. G. (1937): Lancet. 372.